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Review

System approaches of Weiss and Bertalanffy and their relevance for systems biology today

Manfred Drack[a,b,*], Olaf Wolkenhauer[c]

[a] Department of Systems Biology and Bioinformatics, University of Rostock, Germany
[b] Department of Theoretical Biology, University of Vienna, Austria
[c] Stellenbosch Institute for Advanced Study (STIAS), Wallenberg Research Centre at Stellenbosch University, Marais Street, Stellenbosch 7600, South Africa

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ABSTRACT

System approaches in biology have a long history. We focus here on the thinking of Paul A. Weiss and Ludwig von Bertalanffy, who contributed a great deal towards making the system concept operable in biology in the early 20th century. To them, considering whole living systems, which includes their organisation or order, is equally important as the dynamics within systems and the interplay between different levels from molecules over cells to organisms. They also called for taking the intrinsic activity of living systems and the conservation of system states into account. We compare these notions with today's systems biology, which is often a bottom-up approach from molecular dynamics to cellular behaviour. We conclude that bringing together the early heuristics with recent formalisms and novel experimental set-ups can lead to fruitful results and understanding.

1. System – the common theme

"[T]here is no phenomenon in a living system that is not molecular, but there is none that is *only* molecular, either" [1]. This paradigmatic and programmatic statement towards a system approach from Paul A. Weiss needs explanation, which we would like to provide in this article, because it is also related to cancer research. That statement already shows the contrast between the system approach of Weiss and more recent ones, as indicated by one recent definition of systems biology: "The science that discovers the principles underlying the emergence of the functional properties of living organisms from interactions between macromolecules." [2] (Broader descriptions can be found [3], as mentioned in subsection "Today's systems biology".) Even though both early and recent system approaches take the interrelation among parts into account, the differences are worthwhile investigating. Basically, the molecules-only approach ignores morphological form and morphogenesis, which are of salient importance for investigations on cancer, which – after all – is also a phenomenon of development at the tissue level. The works of Weiss and Ludwig von Bertalanffy teach us that it is dubious to explain the behaviour of a living system by investigating molecular interactions on the gene and protein level alone. The two biologists, who influenced each other, were among the first to make the notion of a system operable in biology; Weiss was working experimentally, mostly in the field of developmental biology, while Bertalanffy devoted his efforts to setting up a theoretical biology in which wholeness (aka system) plays a major role. Both used the system concept on a broad variety of biological issues, from cells to organisms and beyond [4–7]. In this article we point out important issues from their copious work which may be relevant to system approaches in cancer research.

2. Motivations for an early system approach

Some works of Weiss and Bertalanffy were supported by cancer research funds, but their main focus was on other areas and they did not explicitly use a system approach for cancer research. Weiss was cautious when it came to cancer research, as he did not directly conduct research in this area. He did, however, point out the importance of considering interactions on various levels, including the environment of the cells [8,9]. Bertalanffy worked on growth in different species [10] and developed a screening method for cancer that involved staining RNA with acridine orange and observing the cells with fluorescence microscopy [11]. Related to cancer research, he performed investigations with hormones [12]. For an overview on Bertalaffy's work, comprising research on malignant growth and diagnostic methods in cancer, see the biography of Pouvreau [13]. The diagnostic method also made him think about a cytoplasmic theory of cancer development, as an alternative to the then contemporary virus and somatic mutation theory of cancer [14].

* Corresponding author at: Althanstraße 14, 1090 Vienna, Austria. Tel.: +43 1 4277 56706; fax: +43 1 4277 9567.
E-mail addresses: manfred.drack@univie.ac.at (M. Drack), olaf.wolkenhauer@uni-rostock.de (O. Wolkenhauer).

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Considering causes of cancer beyond the traditional candidates is reminiscent of the recent tissue organisation field theory [15].

It would be too speculative to state what Weiss and Bertalanffy would have come up with had they thought about cancer with a system perspective, but it is not speculative to report what they said in general about a system approach in biology. Hence, we restrict our investigation to those aspects of their system thinking in biology that are relevant to modern cancer research.

Although the early system thinkers were mostly incognisant of molecular processes at the gene–protein level, they emphasized important characteristics of a whole entity which molecular approaches cannot circumvent. Accordingly, phenomena at the macroscopic level must be reconciled with interactions on the level of molecular interactions. The question of how processes on the micro-scale refer to those on the macro-scale and vice versa is crucial.

Weiss and Bertalanffy were sceptical about a mere mechanistic view of the organism, i.e., the notion of the organism as a machine. More specifically, the analytico-summative approach, i.e., analysing parts and putting this knowledge together, seemed to be limited, and they tried to overcome this by using a system approach. This attitude shaped their scientific approach and experimental work. Putting together the findings from analytic dissection, in reality or in our minds, cannot yield complete explanations of the behaviour of even the most basic living system [1]. The attempt to synthesize the isolated analytic findings step-by-step does not work for systems. Just like in the many-body problem in physics, “the coexistence and cooperation of all [parts] is indispensable for the existence and operation of any one of them” [1]. Weiss exemplifies the simile of an arch consisting of single bricks which is only stable as a whole. Knowledge about order or organisation within the organism can never be retrieved when only fractions of that order are studied. The investigation of isolated parts and processes leaves aside organisation, a primary feature of life, with regard to structure and function. Weiss, however, is against the one-sidedness of both “holism” and “reductionism” because living entities have to be approached from the micro- as well as the macro-perspective [16,17]. In biology a tendency was (and still can be) found to view the organism as being determined by “micromechanical” processes on the molecular level, a standpoint which Weiss clearly contradicts. He argues that not even physicists strictly stick to “microdeterminism,” which refers to the idea that macroscopic phenomena are merely caused or determined by events on the microlevel (microprecise causality) [1]. Within his system approach he instead introduces the concept of macrodeterminacy, which is diametrically opposed to microdeteriminism, as we show below.

Recent developments in systems biology lean heavily on the notion of control and regulation by feedback. Not neglecting the merits of the related field of cybernetics, Bertalanffy criticises its narrowness. Cybernetics can be described as the science of the regulation of systems with “circularity” or “recursiveness” as a central concept. With regard to system theory, Bertalanffy holds that the feedback model is but one, rather special, type of self-regulation in a system [6]. Those self-regulating mechanisms are a subclass of Bertalanffy’s general systems. They cannot be used to explain how the organisation comes about or how it develops. Machines that are steered by feedback mechanisms can allow for material and energy flow within the machine, like in open systems, but other areas of Bertalanffy’s system concept such as growth and development cannot be tackled with mere feedback based on a given structure of interactions. “To be sure, cybernetic systems provided with memory devices can learn, that is, change and increase their organisation owing to information input. They cannot undergo processes of differentiation [. . .]” of their structure [6]. This may be appropriate for many questions. In Bertalanffy’s system theory, however, the development of structure (organisational as well as spatial) is crucial when dealing with basic characteristics of life. “Concepts and models of equilibrium, homeostasis, adjustment, etc., are suitable for the maintenance of systems, but inadequate for phenomena of change, differentiation, evolution, negentropy, production of improbable states, creativity, building-up of tensions, self-realisation, emergence, etc.; as indeed Cannon realized when he acknowledged, beside homeostasis, a ‘heterostasis’ including phenomena of the latter nature.” [18]

3. Concepts of Weiss and Bertalanffy

The agreement about a conceptual basis towards a system understanding in biology between Weiss and Bertalanffy involves dynamics, hierarchies, and wholeness – an epistemological concept directly connected to organisation. These are key concepts for understanding living systems. Additionally, the concepts of primary activity, of conservation of the systems state, and the history of a system are central for their thinking. They emphasise the autonomy of biology and point to the need of finding laws of higher order. In the following, we make these concepts more explicit. Details can also be found in Ref. [7].

Weiss and Bertalanffy’s concept of dynamics in biology involves more than only process regulation on a molecular level. Their dynamic approach also includes systems open with regard to matter and energy. However, very important for a basic understanding of life, and also for cancer research, are the dynamics in development. Their interest in dynamics at the level of changing form over time and growth led to conceptions of dynamic morphogenesis [19]. In contrast to more recent points of departure, their system approaches had, among others, a strong foundation in developmental biology.

The concept of hierarchy is central to the work of Weiss and Bertalanffy. Important here is what they thought about spatial hierarchy, from molecules to the organism and even ecosystems, and the causal relationships between the involved levels. This links to Weiss’s stratification of determining interrelations. Stratified determinism includes both macro- and microdeterminacy, that is, determination goes downward the hierarchical levels from environment over organism, tissue, cytoplasm, nucleus, chromosome to genes as well as upward in the opposite direction [1]. For each level, one has to consider influences from each other level, both from top-down as well as from bottom-up. Hence, explanations of appearances in the organism have to consider more than the mere molecular level. Macrodeterminacy refers to “order in the gross with freedom in the small,” which is, according to Weiss, the prime feature of any system [16]. Put differently, determinacy can be found in the gross (i.e., all higher levels in living systems) despite indeterminacy in the small [1]. Examples stem from developmental biology, where two embryos can look similar while parts of them, initially in the same position, take very different spatial courses throughout ontogenesis. Consequently, systems are characterised by their “stability as a whole” [17]. This concept extends over the hierarchical levels. For instance, the behaviour of a cell is far more invariant and predictable than the vagaries of the constituent organelles and macromolecular clusters [20]. In his own words: “Each subsystem dominates its own subordinate smaller parts within its own orbit of domain, as it were, restraining their degrees of freedom according to its own integral portion of the overall pattern, much as its own degrees of freedom have been restrained by the pattern of activities of the higher system of which it is a part and participant” [1]. In a system, the structure of the whole determines the behaviour of the parts, not vice versa like in a machine [1]. Bertalanffy is very much in line with this notion when

he claims that, physiologically, the whole organism determines the performance of the cells, not the other way round [5].

Weiss suggests the concept of “molecular ecology” [21], which refers to the subordination of molecules to ordered “group coexistence” bridging the gap between physical structure and chemical action [22,23]. Each sort of molecular population can exist only when fitting into a set of external conditions, mainly the physico-chemical milieu and the products and activities of other molecular populations [24]. A cell is neither a “sort of random scramble of molecules, nor [. . .] a rigid stereotyped composite of microstructures, but something in between,” partly fluid and partly consolidated [23]. The heterogeneous populations of molecules that constitute a living cell do not have the degrees of freedom of interaction as in a dispersed state of thermal agitation in a test tube solution [20]. Naturally, the concept of molecular ecology was merely an initial idea that could spawn further investigations. It does, however, reflect the importance of taking into account the spatial and other circumstances in the cell, i.e., the context or environment in which the molecular processes are performed. Spatial structures are also relevant for biochemical reactions, when enzymes are bound to specific sites. The enzyme’s activity then depends on the accessibility to the substrate and the physico-chemical environment in the particular microsite [24]. The geometric configuration of tissues can determine which cells will grow further and which ones will cease to grow [25]. Hence, more that single factors, like growth factors, have to be investigated to find out what determines certain cellular behaviour or behaviour on other levels. Bertalanffy argues along the same line when he talks about the morphological order in the cell [26].

The concept of wholeness clearly plays a major role for both thinkers. This involves taking the whole structure and function of a system into account when investigating living systems. The overall architectural design of a cell “cannot be explained in terms of any underlying orderliness of the constituents” and “the overall order of the cell as a whole does not impose itself upon the molecular population directly, but becomes effective through intermediate ordering steps, delegated to subsystems, each of which operates within its own, more limited authority” [1]. Splitting apart the components of the system and investigating them in isolation will thus always lead to a restricted understanding of biological features. Wholeness is tightly connected to the notion of a system. Weiss defines a system as “a complex unit in space and time so constituted that its component subunits, by ‘systematic’ cooperation, preserve its integral configuration of structure and behaviour and tend to restore it after non-destructive disturbances” [20]. This definition includes another fundamental characteristic of living systems: conservation. In this context, conservation refers to a kind of robustness that helps restore the system after disturbance. Dynamic processes bring the system back into its original state.

Living systems show another important characteristic. In contrast to “monotonic” systems – where only a single modality of dynamics plays a role – living systems are “polytonic,” including other modalities as well, e.g., electric charge distribution, temperature gradients, chemical processes [20]. Hence, many different kinds of interactions can influence the properties and behaviour of a living system. Implicitly this means that a certain behaviour must not be caused by only one instance, like a molecular event, but can be influenced by other instances as well. The concept entails that, for a complete understanding, all the potentially relevant modalities must be investigated.

As noted above, morphology and therefore spatial form plays a major role for Weiss and Bertalanffy. The importance of spatial information is also reflected in Weiss’s development of the concept of morphogenetic organisation fields – ascribing a certain quality, direction, and intensity to points in space. Cells in different places in the organism would then be organised by information that determines the cells differently based on their spatial position. Weiss formulated his field approach in accordance with own experimental findings in developmental biology, especially transplantation experiments. This idea – which has to be distinguished from vitalistic field theories [27] – is once again sparking interest in developmental biology [28]. Weiss [29] suggested that different species not only have different genetic material but also different organising fields. Only when considering the organism as a whole can the part’s dependency on the position be understood. The ordering principles of field continua can be applied at the integral level of a system, that is, for the system as a whole. In contrast, discrete units of the system, like molecules or cells, must also be investigated on their own, differential level. Both complementary approaches are necessary. Weiss states that he has not found any phenomena in a living system which could be described without reference to this dualistic scheme of integral and differential level [1]. According to the dualistic concept, discrete units are “enmeshed in, and in interplay with, an organised reference system” [20].

The behaviour of a living system is also history dependent. Weiss showed this in his experiments on butterflies, where behaviour can be understood more completely when also considering the animal’s past [30]. Already in this 1925 article on butterfly behaviour, Weiss stated the basic premises of his system approach in biology. Of course, the history of biological systems must be considered on different time scales; the long phylogenetic and the shorter ontogenetic time scales are the basic historical components that have to be considered in biology.

After briefly examining the relevant issues in Weiss’s system approach, we now focus on Bertalanffy, who tried to establish the field of theoretical biology, with the system approach at its center. His “organismic” biology is a complementary approach to the anlytico-summative approach. It examines systems or entities as a whole, i.e., the parts and their interrelations. Organisation, or order of substances and processes, is a primary feature of living systems. It must be taken into account to derive sound knowledge about living entities. “The actual essence of life lies in the organisation of the substances and processes [. . .] It is by no means enough for a knowledge of life when we know the single parts and processes in the finest details; we are allowed to speak of such a knowledge only if we know the laws which rule the order of all those parts and processes” [26]. For practical and cognitive reasons, however, this is a complex undertaking. Determining completely a single biological process in an organism calls for knowing all processes it depends on. This seems to be impossible to achieve, as the same holds true for each other process. What can be done, on the one hand, is to isolate a single process and investigate it in a physico-chemical way, but this provides no knowledge about the reciprocal dependences among processes. On the other hand, an event involving the whole organism may be investigated to arrive at principles that are valid for the whole, whereby the physico-chemical determination in the detail is left aside [26]. The second approach to investigation indicates Bertalanffy’s system understanding. It is even more important in cases where the single processes are ordered for the maintenance of the whole [31]. Bertalanffy is not principally against research that is concerned with mere parts and interactions, but clearly points to the problems of such an approach – which also limits our current knowledge. He holds that, in principle, the properties of a higher level are derivable from their components – if we know all the components and all the relations between them [5]. This requires already knowing the organisation beforehand. Knowing all parts and their interrelations in a biological system exceeds our current abilities. Hence, Bertalanffy advocates the search for laws of higher order, a sort of higher order statistics similar to Boltzmann’s thermodynamics [26]. Such laws should provide knowledge about whole biological systems without considering each and every involved detail on a microscopic level. This

presumes that such formal laws, expressed in mathematical terms, can be found. He devoted considerable effort to demonstrating this. In this regard, Bertalanffy's growth equations must be seen as an example of his program and as an important contribution to the rise of the field of mathematical biology. On the one hand, they describe the behaviour of a system on the system level, i.e., on a level of higher order. The equations are suitable to predict the mass of a whole organism during growth. On the other hand, the equations go beyond contemporary data fitting of growth curves, and link growth (and hence morphology) with metabolism. This helps predict growth types from metabolic types [32,33]. It demonstrates the possibility of arriving at knowledge on a higher level, and that data fitting has its limitations.

Bertalanffy derives what he calls general principles or working hypotheses of biological organisation [26,34]. The first principle is that of an open system in flux equilibrium or steady state [26]. Matter and energy is constantly flowing through the system, which more or less remains as it is. This principle is generally accepted for organisms and is expressed in terms of non-equilibrium thermodynamics. Bertalanffy, however, applies this principle to any organic level from cell to biocoenosis. "A given organic system is essentially nothing else than a hierarchical order of stationary flows. What, at any level of the hierarchical order, represents a self-maintaining entity, can be considered as a dynamical equilibrium of subordinated systems which, while the whole maintains itself, are subject to a continuous change; but on the other hand, the system is itself again a transient element of the next higher system" [35]. Spatial structures are seen as prolonged and slow events, whereas functions are temporary and fast events [35]. The second principle is called the principle of hierarchisation or principle of progressive organisation (or individualisation) [26]. The concept of hierarchy involves entities such as molecules, cells, and organisms – static entities so to say. In contrast, hierarchisation is a dynamic process. Throughout development, the dynamic interactions in the system lead to sub-systems of ever more differentiated cells and thus give rise to order, while complexity increases. A third principle is that of primary activity of the organism [35]. Not only are organisms active without stimulus from outside, the same holds true for organs and even cells within an organism. This view stands in contrast to a passive concept of living systems that merely react to stimuli from the outside world. Contrary to the passive concept, such stimuli from outside are regarded to modify the activity of the living system. The organism only secondarily reacts to stimuli from the environment, and those influences only contribute to modifying the organism's activity.

Some of the key concepts of Bertalanffy's thinking (dynamics, hierarchies, wholeness, and conservation) are included in his definition of an organism: a living organism is a system consisting of a large number of different parts, organised in hierarchic order, in which a large number of processes are ordered in such a way that, through their continuous interactions within wide borders, with a continuous change of substances and energies, the system stays, even when disturbed from outside, in its own state, or it builds up that state, or these processes lead to the generation of similar systems [26].

Epistemologically, Bertalanffy, who was also a philosopher, advocates a perspectivism. This is reflected in different instances. First, he holds that biology needs to operate with different methodical perspectives: the physico-chemical, the integrative or organismic (i.e., systemic), the teleological, and the historical perspective [31]. All these perspectives have to be considered when attempting to grasp the phenomena in living nature. A second instance is his growth equations. He attempted to show that the constants used in his growth equations can be derived with different methods which are independent of his model [36]. When the same results converge from different perspectives, objective knowledge can be gained. Pursuing research in only one perspective is therefore insufficient.

4. Today's systems biology

Systems biology is not a product of a single discipline within biology, but is rather based on three different roots within the life sciences: modelling of metabolic and signalling pathways; biological cybernetics and systems analysis; and genomics as well as other "omics" projects [37]. The heterogeneous field of systems biology can be described as the study of the "dynamic interactions between components of a living system, between living systems and their interaction with the environment" [3]. The aim is to understand the consequent function and behaviour of the system, i.e., how a biological whole behaves over time. Although this definition does not restrict systems biology to the molecular level of cells, a large part of it deals with investigations on this level. Many models focus on signal transduction and signalling pathways, trying to determine the dynamic interactions and their relation to cell division, differentiation, and apoptosis. This is driven by measurement data available on the gene and protein level, that is, molecular data from gene expression, phosphoproteomics, epigenetics, and metabolomics. Typically, the models express cell behaviour by means of quantitative concentration changes in the molecular networks, i.e., levels of transcripts and gene products [38]. The formal models, often based on ordinary differential equations, abstract from spatial distributions of molecules and cells and assume a bottom-up causation from molecular dynamics to cell behaviour.

Systems biology is also often explicitly directed towards medical applications [38,39], including cancer research [40]. The challenge lies in identifying and analysing the principles, laws, and mechanisms that underlie the behaviour of biological systems – from genes to tissues across various spatial and temporal scales.

Recently, morphological and spatial features are also attracting interest because cells can function differently with regard to their location. Taking spatial relations into account is necessary because signal transduction pathways can be switched on and off, depending on cell shape and size. Acknowledging that these factors play an important role for modelling also points to the need for experiments that take such features into account. This calls for overcoming the fragmentation on the experimental side [39]. An example for a model that incorporates spatial effects on the cellular level is crypt dynamics: comprising the sub-cellular, cellular and tissue level, this approach binds together a Wnt signalling model, a cell-cycle model and a mechanical model [41]. The need for such models is indicated by findings that point to the relevance of the microenvironment of stem cells in colon cancer [42]. As noted above, regulation based on feedback plays an important role in current systems biology, mainly on the molecular level. However, the feedback concept is also introduced on other levels. An interesting example is the definition of stem cells via feedback signals among adjacent cells, that is, the environment determines the behaviour of the cell [43].

Although systems biology research has only recently started, eminent system thinkers have already pointed out the problems regarding the narrowness of its current conceptual framework. Physiologist Noble advocates "downward causation" (not a new term [44]) as an important issue that needs to be considered within the field of systems biology, where a causal connection is often emphasised in only one direction (e.g., from genes to proteins to cells, etc.) [45]. Mesarović, who already in 1968 coined the term "systems biology," was sceptical about applying only engineering principles to biological problems because certain characteristics of living entities have to be taken into account which engineering does not consider [46,47]. The question remains whether today's systems biology neglects basic characteristics of the organism and

oversimplifies [48]. Systems biology itself, however, is a heterogeneous field, and the critique does not apply to the whole field.

5. Comparison and conclusion

Clearly, the point of departure of Weiss and Bertalanffy was different from that of today's systems biology. Weiss and Bertalanffy used the system approach, complementary to the analytico-summative approach, to gain a basic understanding of biological issues. This was often motivated by findings in the field of developmental biology. Systems biology has its roots in new experimental and measurement methods, and aims for a dynamic understanding of the behaviour of mostly small systems. Broadly speaking, Weiss and Bertalanffy started from the whole and saw it as a system, while systems biology started from the parts and works on ever more inclusive systems.

O'Malley and Dupré [49] distinguish two types of approaches. The first one is referred to as "systems-theoretic biology," which strives for laws or fundamental principles. The second is termed "pragmatic systems biology" of the post-genomic era, where high-tech tools and sophisticated computational models are utilised to study the interplay between the parts (mostly molecules) of a living system. Parallel to this laboratory approach to systems biology, research on "systems-theoretic biology" is urgently needed to help provide stronger explanatory power, which, according to Krohs and Callebaut [37], is lacking in today's systems biology. Many questions in systems biology still remain open with regard to philosophy of science, epistemological as well as ontological questions. No epistemology is available that takes into account the evolutionary and developmental history of biological entities [50]. The book of Boogerd et al. [51] is a step towards an in-depth discussion of philosophical issues in systems biology. Those philosophical considerations are not only interesting in themselves. They are also relevant for understanding and explanation in biology.

Compared to recent methods in systems biology, the drawback of Weiss and Bertalanffy's approaches is that they are mostly heuristic and do not provide readily available formal tools. Bertalanffy tried to incorporate several concepts that seemed important to him into a formalism, but did not get very far. This makes their approaches different to readily usable system theory based on engineering or the dynamic systems approach: these are formalised and follow a strict method, but at the same time leave out issues that are important in biology. The system approach of Weiss and Bertalanffy must be reconciled with approaches in systems biology; the former start with the whole, the latter with the dynamically interacting parts. Only when knowledge from both approaches fit together are the results valuable. This is also important for cancer research because cancer goes beyond a molecules-only phenomenon to a developmental phenomenon.

Important tasks remain to be tackled in the future. Living systems are polytonic, as Weiss proposes, and this calls for determining which factors influence an observed system and which do not. The experimental hurdle is to investigate simultaneously phenomena on different levels. Disciplinary borders must also be crossed in biology. This approach also entails methodical difficulties in mathematics and computation. The mathematical formalism, however, is not bound merely to molecular interactions, but can also be applied on other levels.

The pioneers would probably not have neglected the system approach of today's systems biology, but they may well have found to be too narrow. Some strands of systems biology seem to continue a molecular course of genetics and biochemistry by making it dynamic, without touching on form and other issues on levels beyond the molecules. Bringing together the early heuristics with experiments and formalisms of recent systems biology is therefore an important task for the future.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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